REMARKS

Claims 1-19 were previously pending in this application. Claims 1-7 and 12-19 have been withdrawn from consideration as being drawn to non-elected subject matter. By this amendment, claims 1-7 and 12-19 have been cancelled without prejudice to the filing of any appropriate divisional/continuation application as being directed to non-elected subject matter. New claims 20-32 have been added to claim additional embodiments of the invention. The number of pending claims is below the original number of claims, so no fee should be required for their entry. No new matter has been added.

Claims 8-11 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Claims 8-11 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Claims 8-11 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants gratefully acknowledge that the Office Action states that the prior art of record, taken individually or in combination, did not suggest or render obvious the subject matter of claims 8 to 11.

Applicants have amended the claims to more clearly define and distinctly characterize Applicants' novel invention. Specifically, claim 8 was amended to recite that the TGR183 polypeptide is activated by nicotinic acid. Support for this amendment can be found in the instant specification at least at paragraphs [0205] and [0206], where Applicants teach that nicotinic acid is a ligand that activates TGR183.

Applicants also have presented new claims 20-32 for consideration. Claims 20-24 are dependent claims which increase the level of sequence identity to 75%, 80%, 85%, 90% or 95%, respectively. Claim 25 specifies the actual sequence of SEQ ID NO:6 and claims 30-32, which parallel the recitations of original claims 9-11, depend on claim 25. Claims 26-29 are dependent claims which increase the number of contiguous amino acids to 30, 40, 50 or 100, respectively. Support for these claims is found *inter alia* at paragraph [0035] of the instant specification and in original claims 9-11.

The amendments presented herein add no new matter and do not raise new issues requiring further search. Applicants respectfully request entry and consideration of the foregoing

amendments, which are intended to place this case in condition for allowance.

Objections to the Specification

At page 2, section 3 of the Office Action, the title and abstract are objected to because they do not describe the invention now claimed. The Office Action states that a revised title and abstract reflecting the specific features of the claimed invention needs to be provided. In response, Applicants respectfully submit that the title and abstract have been amended to recite TGR183 receptor ligands and TGR183 receptors. Accordingly, Applicants request that these objections be reconsidered and withdrawn.

The Specification Provides Adequate Written Description for Claims 8-11

At page 4, section 5 of the Office Action, claims 8-11 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action states that the instant specification does not provide an adequate written description of the genus of proteins encompassed by the term "TGR183" as that term is defined in the specification. The Office Action further states that considering the large genus of proteins that could potentially be encompassed by the term "TGR183," the description of a single, naturally occurring species within that genus does not constitute a written description of a representative number of species within that recited genus. Applicants respectfully traverse this rejection based on the amended claims now presented.

Without acquiescing to the rejection, Applicants respectfully submit that claim 8 has been amended to include the ***functional characteristic*** wherein the claimed TGR183 polypeptides are ***activated by nicotinic acid***. Specifically, amended claim 8 and claims depending therefrom are directed to a method of identifying a modulator of a TGR183 polypeptide that has G-protein coupled receptor activity and comprises at least 70% amino acid sequence identity to SEQ ID NO:6, comprises at least 20 contiguous amino acids of SEQ ID NO:6, or comprises the amino acid sequence of SEQ ID NO:6, wherein the method comprises contacting a compound with a

recombinant TGR183 polypeptide, and determining the level of binding of nicotinic acid to the TGR183 polypeptide in comparison to the level of binding in the absence of compound. Applicants have discovered that nicotinic acid is the natural ligand of TGR183 polypeptides (specification, paragraphs [0205] and [0207]).

The first paragraph of 35 U.S.C. § 112 requires that the specification provide a written description of the claimed invention:

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). With respect to polypeptides, the U.S. Patent and Trademark Office's Written Description Guidelines state:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by . . . disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus . . . .

66 Fed. Reg. 1099, 1106 (January 5, 2001), internal reference omitted, approved in *Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 296 F.3d 1316, 1325, 63 U.S.P.Q.2d (BNA) 1609, 1613 (Fed. Cir. 2002) (emphasis added).

Applicants respectfully submit that the specification more than adequately describes the claimed methods with reasonable clarity to one of skill in the art. Applicants teach the amino acid sequence of human TGR183 (SEQ ID NO:6), the nucleic acid sequence of human TGR183 (SEQ ID NO:5), and teach that other TGR183 nucleic acid and protein sequences have been

described (specification, paragraph [0027]). Applicants teach that a sequence identity in the context of polypeptide sequences refers to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same over a specified region when compared and aligned for maximum correspondence over a comparison window or designated region as measured using a BLAST or BLAST 2.0 sequence comparison algorithm or by manual alignment and visual inspection (specification, paragraph [0075]). Thus, one of skill in the art would recognize that the specification adequately describes the claimed TGR183 sequences.

At the time of filing of the subject application, a plethora of G-protein coupled receptors had been identified and characterized as a large superfamily of related receptor molecules that play a key role in many signaling processes, such as sensory and hormonal signal transduction (specification, paragraph [0004]). Those of skill in the art would recognize that G-protein coupled receptor superfamily members share an ***overall structure*** that is well-characterized and typically includes seven transmembrane domains, an extracellular amino terminus and an intracellular carboxy terminus (specification, paragraph [0004]). Accordingly, one of skill in the art, based on Applicants' teachings and the knowledge in the art at the time of filing, would readily understand the structure of a G-protein coupled receptor.

Applicants further teach that a G-protein coupled receptor activity refers to the ability of the G-protein coupled receptor to transduce a signal, and teach that such activity may be measured by recording ligand-induced changes in $[Ca^{2+}]_i$ using, e.g., fluorescent Ca^{2+}-indicator dyes and fluorometric imaging (specification, paragraph [0041]). Applicants teach that nicotinic acid activates TGR183 polypeptides, and describe specific experiments wherein a G-protein coupled receptor activity was assayed: an Aequorin assay was performed to assess the ability of nicotinic acid to activate TGR183, resulting in the mobilization of intracellular calcium (specification, paragraphs [0205]-[0206]). Thus, one of skill in the art would understand that the specification sufficiently describes the claimed G-protein coupled receptor activity as well as activation of a TGR183 polypeptide by nicotinic acid.

The specification must be considered as a whole when determining whether the written

description requirement is met. *In re Wright*, 866 F.2d 422, 425, 9 U.S.P.Q.2d (BNA) 1649, 1651 (Fed. Cir. 1989). The knowledge of one skilled in the art also must be considered, because the specification must "indicate[s] to persons skilled in the art that as of the [filing] date the applicant had invented what is now claimed." *All Dental Prodx LLC v. Advantage Dental Products Inc.*, 309 F.3d 774, 779, 64 U.S.P.Q.2d (BNA) 1945, 1948 (Fed. Cir. 2002). We submit that the level of skill is quite high in this technology. When read as a whole, taking into account the knowledge of persons skilled in the art at the filing date of the subject application, this specification indicates to those skilled in the art that Applicants had possession of the claimed subject matter at the time of filing. Accordingly, the Examiner is respectfully requested to reconsider and withdraw this rejection of claims 8-11 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Claims 8-11 Are Enabled

At page 2, section 4 of the instant Office Action, claims 8-11 stand rejected under 35 U.S.C. § 112, first paragraph, because the claims encompass subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office Action states that the specification does not provide the guidance needed to practice the claimed process with a "TGR183" polypeptide comprising anything less than the entire amino acid sequence presented in SEQ ID NO:6. The Office Action further states that one of ordinary skill in the art of receptor biology would not reasonably believe that the majority of physical peptide embodiments having at least 70% sequence identity to SEQ ID NO:6, or at least 20 contiguous amino acids thereof are going to be functional, much less be capable of producing an authentic response. Applicants respectfully traverse this rejection based on the amended claims now presented.

35 U.S.C. § 112, first paragraph requires that the specification must enable a person skilled in the art to make and use the claimed invention. However, a specification need not, and should not, disclose what is well known in the art. The invention that one skilled in the art must be enabled to make and use is that defined by the claims of the particular application. The issue

of adequate enablement depends on whether one skilled in the art could practice the claimed invention without undue experimentation. Enablement is not precluded by the necessity of some experimentation such as routine screening, even if it is extensive routine screening. Also, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (MPEP 2164.01) if the level of skill in the art is high or if all of the methods needed to practice the claimed invention are well known. *In re Wands*, 8 U.S.P.Q. 2d 1400, 1406 (Fed. Cir. 1988).

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. (Citations omitted). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 U.S.P.Q. 2d at 1404.

Without acquiescing to the rejection, Applicants respectfully submit that the amended claims include the distinguishing feature that the claimed TGR183 polypeptides are activated by nicotinic acid.

Furthermore, Applicants are not claiming the genus of TGR183 polypeptides, *per se*. Rather the claims are directed to methods of identifying modulators of such peptides. Applicants have shown multiple species of such polypeptides and have provided ample teachings for identifying additional species using, what in this technology can only be described as, routine testing. Nothing more should be necessary to enable the claimed methods.

In any event, Applicants need not claim specific positions in the protein which are tolerant to change, or the nature and extent of changes that can be made in specific positions to enable the claimed method invention, as one of skill in the art would easily recognize the claimed TGR183 polypeptides having both the claimed sequence identity and the claimed functional characteristic of activation by nicotinic acid. Determining whether a TGR183 polypeptide has the claimed sequence identity or the claimed contiguous amino acids, has a G-protein coupled receptor activity, and is activated by nicotinic acid would involve only ***routine screening***. For at least the reasons set forth above, Applicants respectfully submit that the specification teaches the amino acid and nucleic acid sequences of human TGR183, that the

sequences of other TGR183 polypeptides were known in the art at the time of filing, and that the claimed amino acid sequences have a specific amino acid sequence identity (i.e., comprising a percent identity to SEQ ID NO:6, consisting of at least 20 contiguous amino acids of SEQ ID NO:6 or comprising the amino acid sequence of SEQ ID NO:6). Applicants teach how to isolate nucleic acids encoding G-protein coupled receptors (specification, paragraphs [0093] to [0100]), how to purify G-protein coupled receptors (specification, paragraphs [0118] to [0121), and how to immunologically detect G-protein coupled receptors (specification, paragraphs [0122] to [0135]). Further, Applicants teach a screening method in which TGR183 polypeptides that have a G-coupled receptor activity and are activated by nicotinic acid may be identified (discussed above). Accordingly, based on these teachings, one of skill in the art could easily make and use the claimed TGR183 polypeptides.

For at least the reasons set forth above, Applicants' specification, coupled with the level of skill in the art, enables a person of skill in the art to make and/or use the claimed invention. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 8-11 under 35 U.S.C. § 112, first paragraph, as lacking enablement.

Claims 8-11 Are Definite

At page 6, section 6 of the instant Office Action, claims 8-11 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office Action states that these claims are vague and indefinite insofar as they employ the term "TGR183" as a limitation. The Office Action further states that, because the instant specification does not identify that property or combination of properties which is unique to and, therefore, definitive of a "TGR183" polypeptide, an artisan can not determine if a compound which meets all of the other limitations of a claim would then be included or excluded from the claimed subject matter by the presence of this limitation. Applicants respectfully traverse this rejection based on the amended claims now presented.

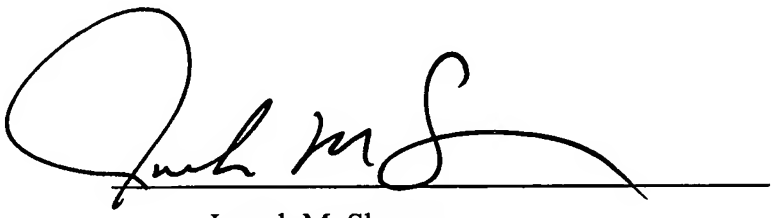
Without acquiescing to the rejection, Applicants respectfully submit that amended claim 8 recites a method for identifying a modulator of a TGR183 polypeptide that has a ***G-protein***

coupled receptor activity and is ***activated by nicotinic acid***, and ***comprises at least 70% amino acid sequence identity to SEQ ID NO:6***, comprises ***at least 20 contiguous amino acids of SEQ ID NO:6***, ***or*** comprises ***the amino acid sequence of SEQ ID NO:6***. Thus, the pending claims recite the defining characteristics that the claimed TGR183 polypeptide has a G-protein coupled receptor activity, is activated by nicotinic acid, and comprises a particular amino acid sequence. Accordingly, the pending claims clearly recite a combination of properties which is unique to and, therefore, definitive of a TGR183 polypeptide. Accordingly, Applicants respectfully request that this rejection of claims 8-11 under 35 U.S.C. § 112, second paragraph, as being indefinite be reconsidered and withdrawn.

Conclusion

Having addressed all outstanding issues, Applicants respectfully request entry and consideration of the foregoing amendments and reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,



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Joseph M. Skerpon
Registration No. 29,864

BANNER & WITCOFF, LTD.
1001 G Street, N.W.
Washington, D.C. 20001
Telephone: (202) 824-3000